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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/002,050

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Richard A. Shimkets

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(Cura-5)

7590

10/16/2003

EXAMINER

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ART UNIT

PAPER NUMBER

1642

DATE MAILED: 10/16/2003

11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/002,050

Applicant(s)

SHIMKETS ET AL.

Examiner

Larry R. Helms

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) 16 and 17 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to:
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-15 in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
2. Claims 15-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Election was made without traverse in Paper No. 10.
3. Claims 1-15 are under examination.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

- a. Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The citizenship for John Herrmann has been changed.

Specification

5. The disclosure is objected to because of the following informalities:
- a. The first line of the specification should indicate that the instant application is a CON of 09/604,286.
 - b. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see for example page 10, line 21. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.
 - c. The brief description of the drawings should indicate Figure 15A-C and Figure 20A-C.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:
- The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
7. Claims 3-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
- a. Claims 3-6 and 9 are indefinite for reciting "its complement" in claims 3 and 4 because it is unclear how a polypeptide can have a complement.
 - b. Claim 5 is indefinite for reciting "mature form" because the exact meaning of the phrase is not clear. The specification discloses a "mature protein" arising as a result of post-translational modifications (see page 18, line 21-22). Does this mean those

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modifications as a result of the cellular processes or those modifications as a result of chemical modifications outside a cell? In addition, does the phrase mean a properly folded protein where the "mature form" is a folded protein as opposed to a denatured protein?

c. Claims 7-8 are indefinite for reciting "hybridizes under stringent conditions" because the exact meaning of the phrase is not clear. These conditions appear to be incomplete by lacking washing conditions, accordingly the claims encompass a range of parameters. Moreover, it is not clear whether these conditions are high or low stringency conditions. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 1-15 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

Claims 1-15 are directed to an nucleic acid molecule, oligos, vectors, cells, method of producing a polypeptide and the polypeptide is a peptide selected from the group of a mature form of SEQ ID NO:14, a variant, SEQ ID NO:14, and a variant of SEQ ID NO:14. The specification discloses the SEQ ID NO:14 as SEC 7 and based on sequence similarity SEQ ID NO:14 is asserted to be a novel human semaphorin (see

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page 18). Based on the structural similarity, the specification asserts that the newly disclosed semaphorin has the utility of having similar activities.

The assertion that the disclosed semaphorin has biological activities similar to known semaphorins is not substantial in the absence of supporting evidence, because the relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF- β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF- β family members BMP-2 and TGF- β 1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF- β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone

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14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene

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superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted credible, specific and substantial utility of growth factor activity.

The specification does not support a substantial utility regarding the claimed nucleic acids encoding SEQ ID NO:14 or a variant for purposes unrelated to the asserted biological activity. For example, the specification asserts that the claimed nucleic acids can be used in tissue typing (see page 67), antagonist or agonist in screening combinatorial libraries (see page 42), generate peptide libraries (see page 43), generate antibodies (see page 43-44), screening assays and detection methods (see page 58), pharmacogenomics (see page 76). The specification does not disclose a correlation between any specific disorder and an altered level or form of the polynucleotides or polypeptides. Also, the specification does not predict whether the polynucleotides or polypeptides would be overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control. The specification

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contains assertions that the polynucleotides, polypeptides and the antibodies produced from such can be used the above mentioned areas, however, no specific disease has been associated with the polynucleotides or polypeptide and the asserted utilities are not specific to the polypeptide and the claimed antibodies.

In fact as evidenced from Behar et al (Nature 383:525-528, 1996) the semaphorins "have widespread roles in embryonic development. Some seem to guide neuronal growth cones, but otherwise their functions are unknown" (see page 525). In addition, Furuyama et al (The Journal of Biological Chemistry 271:33376-33381, 1996) states that semaphorins may play a role in the immune system as well as in the nervous system (see abstract). Moreover, Messersmith et al (Neuron 14:949-959, 1995) states that the full range of effects of the semaphorin family remains to be determined and in fact nothing is known about the receptors for the semaphorin family (see page 957). Thus, the references demonstrate that the semaphorins are a diverse family and their exact functions are not known or the receptors for which they interact with if any.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-15 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

12. Claims 11-12 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 11-12, as written, do not sufficiently distinguish cells as they exist naturally because claims do not particularly point out any non-naturally occurring differences between the claimed cells and the structure of naturally occurring cells. Since the nucleic acid can be in a retroviral vector (see page 52) and the vector is integrated into the genome, the claims read on a human. In the absence of the hand of man, the naturally occurring cells are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967),

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155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "an isolated" or "purified" cell or similar language would obviate this rejection.

13. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Even if one had a utility for the claimed nucleic acids, one would not be enabled for such due to the breadth of the claims. The claims are broadly drawn to a polynucleotide encoding SEQ ID NO:14 or a nucleic acid that is 90% identical to SEQ ID NO:14, or SEQ ID NO:14 with conservative substitutions, or fragments, or a mature form of SEQ ID NO:14, or a variant of SEQ ID NO:14 and pharmaceutical compositions comprising such, vectors, cells and a method of producing such. The specification discloses SEQ ID NO:14 and the DNA encoding such as SEQ ID NO:13. The

specification discloses a "mature protein" arising as a result of post-translational modifications (see page 18, line 21-22). The specification fails to describe or teach any modification to SEQ ID NO:14 encompassed by a post-translational modification or any variant which has conservative substitutions, or any variant of such or the use of any fragments which reads on a single base in the DNA or RNA. The specification does not teach an activity for SEQ ID NO:14.

The claims are broadly drawn to variants, mutants, conservative substitutions in the protein wherein the specification has not determined an activity or where substitutions can take place in the protein and still retain an "active" molecule or those nucleic acids that are 90% and still function as SEQ ID NO:14. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411

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(1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art.

Claim 13 is drawn to pharmaceutical composition comprising a nucleic acid. Enablement of a "pharmaceutical composition" is considered to rest on a teaching of in vivo administration for purposes consistent with the intended use disclosed in the specification. The use of pharmaceutical compositions comprising inhibitory (antisense) or stimulatory (sense DNA introduced into a deficient cell) forms of nucleic acids, as disclosed in the specification at page 82 for gene therapy is well known in the art to be highly unpredictable, even though the level of skill in the art is high. For instance, Mountain reviews in TIBTECH (18:119-128 2000) that while much progress has been made in the field of gene therapy, developing effective gene therapies is much more demanding than originally anticipated (e.g., pg 120, middle); and that most of the difficulty lies with the development of effective vectors since the vectors in use all have both advantages and disadvantages (e.g., Table 4). Mountain concludes that it is unlikely that a universal vector will emerge in the next few years (page 125, middle of 1st column). Similarly, although antisense therapy has progressed in recent years, there is

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still a high level of unpredictability in the art. This unpredictability was summarized recently by Branch (TIBS 1998; 23:45-50). In particular, difficulties in ensuring that the oligo interacts with its single gene target versus other genes, and a variety of unexpected non-antisense effects, complicate the use of antisense compounds (e.g., summarized in Abstract). Thus in the absence of working examples or detailed guidance in the specification, the intended uses of any pharmaceutical composition comprising an nucleic acid are fraught with uncertainties.

In addition, claim 11 encompasses a transgenic mammal including a human and as such the specification clearly does not teach enablement for transgenic animals with SEQ ID NO:13 or encoding SEQ ID NO:14. Applicants broadly claim a transgenic cell containing a nucleic acid that encodes SEQ ID NO:14 within an expression vector and a method for producing the said polypeptide by culturing the transgenic cell. These claims read on a cell within a transgenic animal given that the term "isolated" is not denoted in describing the transgenic cell. The breadth of the claim reads on the implementation of the transgenic cell in both *in vitro* and *in vivo* assays.

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. Thus, at the time of filing, the phenotype of a transgenic cell contained within any animal was unpredictable and could not be prepared for any species. Applicants can obviate this part of the instant rejection by amending the claim to recite the term "isolated" before the recitation, "cell".

In view of the lack of predicatability in the art, lack of guidance, lack of examples, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

14. Claims 1-3, 5-6, 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to nucleotide sequences that are 90% to DNA encoding SEQ ID NO:14, polypeptides with conservative substitutions in SEQ ID NO:14, mutants and variants of SEQ ID NO:14 and a mature form and DNA encoding such. The specification only discloses SEQ ID NO:13 for a nucleotide sequence which encodes the polypeptide of SEQ ID NO:14. The specification contemplates variants as homologs, naturally occurring variants and derivatives (see pages 25-27). The specification does not teach any such "variants" or any modification to obtain a "mature" form. The general knowledge in the art concerning variants does not provide any indication of how the structure of one variant is representative of unknown variants. Reiger et al. (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome... and differing

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from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:13 and 14 the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides or polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by the Boehringer Mannheim Biochemicals catalog, p 557, 1991.

The claims recite an oligonucleotide that is complementary to and hybridizes to the nucleic acid encoding SEQ ID NO:14 or complementary to SEQ ID NO:13, and a portion thereof.

The Boehringer Mannheim Biochemicals catalog teach random primers which would inherently hybridize to SEQ ID NO:13 or a variant or hybridize to a nucleic acid that encodes SEQ ID NO:14 under the recited conditions.

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17. Claims 3, 6, 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Inkagaki et al (FEBS Lett. 370:269-272, 1995).

The claims recite a nucleic acid that encodes a variant of SEQ ID NO:14, or an isolated nucleic acid that is complementary to at least a portion of the nucleic acid of claim 3.

Inagaki et al teach a polynucleotide that would encode a variant of SEQ ID NO:14 (the term variant is being interpreted in its broad sense to mean any sequence different from SEQ ID NO:14 which encompasses any changes in the amino acid sequence). See the attached sequence alignment on the back of this Office action.

Conclusion

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.


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20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879



LARRY R. HELMS, PH.D.
PRIMARY EXAMINER